**Statement**
**Before the Subcommittee on Retirement and Aging**
**Committee on Health, Education, Labor, and Pensions**
**United States Senate**

# Alzheimer's Disease Research at the National Institute on Aging


*Statement of*
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Senator Mikulski and Members of the Committee:

Thank you for inviting me to appear before you today to discuss Alzheimer's disease (AD), an issue of interest and concern to us all. I am Dr. Richard Hodes, Director of the National Institute on Aging (NIA), the lead federal agency for Alzheimer's disease research. NIA is one of the 27 Institutes and Centers that comprise the National Institutes of Health (NIH), an agency of the U.S. Department of Health and Human Services (HHS). I am delighted to be here today to tell you about the progress we are making toward understanding, treating, and preventing AD.

Dr. Zerhouni's statement cites the number of Americans whose lives are deeply affected by AD. The numbers are indeed stark and are growing with the aging population. But there is another part of the Alzheimer's story that we can tell; although AD remains a major public health issue for the United States, we have made, and are continuing to make, dramatic gains in our ability to understand, diagnose, and treat the disease. This progress offers us hope of reversing the current trends so that the risk of AD can be reduced for millions of older adults and their families.

As the lead Federal agency supporting AD-related research, the National Institute on Aging conducts and supports a portfolio of research that encompasses topics across the spectrum of AD-related inquiry. Active areas of research include basic brain biology, preclinical and clinical research on potential interventions, and population-based assessment of the epidemiology, economic, social and psychological costs of dementia to the family and society. Our research agenda is broad, and we pursue that agenda in partnership with scientists across the

Nation. In October 2006, NIA convened a major scientific planning meeting to discuss future directions for Alzheimer's disease research at NIH, with particular attention to research issues that need to be addressed in order to improve diagnosis and treatment of AD. This meeting brought together internationally-recognized experts in the field, and the results will influence the direction of the research we support over the next few years.

## Risk Factors and Early Diagnosis

Identification of risk factors for AD may enable us to develop interventions to delay or even prevent its onset, and NIA-supported researchers are making important advances in several key areas.

*Genetics.* Discovery of risk factor genes will help illuminate the underlying disease processes of AD, open up novel areas of research, and identify new targets for drug therapy. Researchers recently determined that variations in a gene known as SORL1 may be a risk factor for the development of late-onset AD. While this discovery provides a new genetic clue about the late-onset forms of AD, further research is needed to determine the role of SORL1 in AD pathogenesis.

Research is continuing in this important area through the AD Genetics Initiative, which to date has recruited nearly 1,000 families to establish a resource for studies of the genetics of late-onset AD. In addition, NIA has established a national genetics data repository to facilitate access by qualified investigators to genotypic data for the study of the genetics of late-onset AD. Investigators have already begun submitting data to this repository and requesting additional data

for genetic studies. We also expect genome-wide association studies, mentioned by Dr. Zerhouni, to provide important information about AD's genetic underpinnings.

*Health Conditions Affecting Risk.* Population studies suggest that conditions affecting cardiovascular and cerebrovascular systems may be associated with higher risk for dementia or that the presence of vascular disease may influence the progression of AD. One recent report indicated that AD dementia may be exacerbated by other cerebrovascular problems such as small strokes, while another linked untreated high blood pressure in mid-life with increased risk of dementia in later life. The possible association of diabetes, insulin resistance, and AD is garnering increased attention as well. Recent findings from at least four long-term studies link diabetes with decline in cognitive function. The NIA is currently supporting three clinical trials to examine directly whether diabetes-related interventions might be effective in preventing or delaying cognitive decline or development of AD or AD progression.

*Early Diagnosis: Advances in Neuroimaging.* Research suggests that the earliest AD pathology begins to develop in the brain long before clinical symptoms yield a diagnosis. Therefore, it is critical that we find a way to detect signs of the disease at the earliest point possible so that we can test interventions and, ultimately, treat the disease as early as we can. Toward that end, the NIA has embarked on ambitious efforts to find new ways to measure AD changes in the brain or in other systems including blood and cerebrospinal fluid. These programs are already yielding results. Improvements in brain imaging, coupled with the development of more sensitive cognitive tests, are enabling us to diagnose AD in the research setting with greater precision than ever before. The discovery of compounds such as Pittsburgh Compound B and,

more recently, FDDNP that enable the visualization of AD's characteristic amyloid plaques and neurofibrillary tangles in the living brain – an impossibility only a few years ago – will not only enable scientists to diagnose AD earlier, but may also help researchers and clinicians develop new treatments and monitor their effectiveness, as well as reduce the time and cost of clinical trials.

Research in this area has been intense and productive. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is currently the major venue for facilitating neuroimaging research relevant to AD. Early results from ADNI show that, in addition to aiding early diagnosis, researchers may be able to reduce the time and expense associated with clinical trials by improving methods and developing uniform standards for imaging and biomarker analysis. For example, one ADNI study found that a standard physical model can be used successfully to monitor performance of MRI scanners at many different clinical sites; this will help ensure accuracy of the MRI images produced from ADNI volunteers. Investigators on another ADNI study compared changes over time in PET scans of brain glucose metabolism in people with normal cognition, mild cognitive impairment, and AD, and they found that scans correlated with symptoms of each condition and that images from different clinical sites were consistent across sites, suggesting the validity of PET scans for monitoring the effectiveness of therapies in future clinical trials. This study will continue to provide a foundation for future efforts to identify biomarkers.

An important achievement of ADNI is the creation of a publicly accessible database available to qualified researchers worldwide. The database contains thousands of MRI and PET scan brain images and clinical data and will include biomarker data obtained through blood and

cerebrospinal fluid analyses. ADNI includes samples and brain scans from 200 people with Alzheimer's, 400 people with mild cognitive impairment and 200 cognitively healthy people. All volunteers are between ages 55 and 90. Confidentiality of the participants is rigorously protected. To date, over 200 researchers have signed up for database access.

**Translational Research: Moving Basic Findings into Clinical Practice**

New findings about AD's characteristic pathology are leading to insights that may eventually inform treatment strategies. Amyloid and amyloid-producing enzymes, tau, oxidative damage to the brain, and mediators of inflammation are all under consideration as treatment targets, and investigators are also looking at new ways to protect brain cells as they age and to validate ways to enhance memory and improve cognition with age. For example, recent discoveries have provided support for the validity of beta-secretase (BACE1) as a therapeutic target. BACE1 comes from a family of enzymes known as secretases that cut, or cleave, the amyloid precursor protein (APP) in the brain; working in concert with a partner enzyme, gamma secretase, BACE1 is responsible for the formation of amyloid in AD. In a recent study, NIA-supported investigators were able to silence the production of BACE1 in mice that were genetically engineered to develop AD-like pathology. They found that reducing BACE1 levels slowed the production of amyloid plaques and diminished the damage to neurons and synapses in the brains of the mice receiving the treatment. Notably, the mice in which BACE1 production was halted had less difficulty learning a new task than control mice. NIA's Translational Research Initiative aims to speed research across the continuum of intervention development, from drug discovery to full-scale clinical trials. Components of the effort include grant solicitations to stimulate the discovery, development, and preclinical testing in cellular, tissue,

and animal models of novel compounds for the prevention and treatment of the cognitive impairment and behavioral symptoms associated with AD. The ultimate goal of this initiative is to facilitate submission of investigational new drug applications to the Food and Drug Administration so that more clinical trials testing promising therapies can be started. NIA also supports toxicology services for investigators or small companies that have a potentially viable candidate drug for AD treatment but lack the resources to begin the formal drug testing process.

In addition, NIA is currently supporting approximately 25 AD-related clinical trials. These include studies of:

- Physical exercise, which epidemiological studies suggest may have a specific influence on aspects of cognitive decline. Small clinical trials are currently testing the effects of exercise on cognitive decline and brain function, both in older adults with normal cognition and in persons with mild cognitive impairment with memory decline.
- Statins, which lower cholesterol levels, to determine whether these drugs can modify disease progression in people with mild AD.
- Valproate, which is used to treat epilepsy and some psychiatric disorders, to determine whether this drug can slow decline or help delay the agitation and psychosis that often accompany AD.

Dr. Zerhouni mentioned in his statement that the Alzheimer's Disease Cooperative Study will implement several new clinical trials over the next six years. One, a study to determine

whether docosahexaenoic acid (DHA), an omega-3 fatty acid, will slow cognitive decline in AD, has begun recruitment. Other trials planned by the ADCS include:

- *Intravenous Immunoglobulin (IVIg).* IVIg, a form of passive immunization, contains naturally-occurring antibodies against beta-amyloid, and preliminary studies have shown that IVIg promoted clearance of beta-amyloid from cerebrospinal fluid, as well as improved cognition in AD. The new ADCS trial will demonstrate whether IVIg is useful clinically for treating AD.
- *Lithium.* Lithium, commonly used to treat bipolar disorder, has been shown in animal studies to block abnormal changes in tau and to regulate beta-amyloid. ADCS investigators will undertake a pilot biomarker study to see whether the drug can lower tau and beta-amyloid levels in cerebrospinal fluid and be safely tolerated in older AD patients.

We have also been encouraged by several recent studies related to AD prevention and the maintenance of cognitive health in old age. In 2006, results from the Active Cognitive Training for Independent and Vital Elderly (ACTIVE) study demonstrated for the first time in a randomized, controlled trial that certain mental exercises can offset some of the expected decline in older adults' thinking skills and show promise for maintaining cognitive abilities needed to do everyday tasks such as shopping, making meals, and handling finances. Some of the benefits of the short-term training tested in this study lasted for as long as five years. Investigators also recently announced the discovery of the first agent shown to delay the clinical diagnosis of Alzheimer's in people with amnestic mild cognitive impairment (MCI), an MCI subtype strongly correlated with the later development of AD. The investigators found that individuals who took

the drug donepezil (Aricept®) were at reduced risk of progressing to a diagnosis of Alzheimer's disease during the first year of the trial. In addition, there was benefit over a longer two-year period that was limited to those individuals positive for the APOE-4 gene allele, which confers a strong predisposition to the development of late-onset AD. Although donepezil's effects were limited, the results are nonetheless encouraging. And although too little is known about donepezil's long-term effects to support a recommendation for its routine use to forestall the diagnosis of AD in people with mild cognitive impairment, these findings do suggest that chemoprevention of AD is possible and support our hope that future clinical studies will lead to more significant progress.

## Caregiver Support

Most Americans with AD today are cared for outside institutional settings by an adult child or in-law, a spouse, another relative, or a friend. Research has shown that the stress of caring for a loved one with AD can have a profoundly negative impact on health and well being. NIA-supported investigators have found that a personalized intervention consisting of home visits, structured telephone support sessions, and telephone "check-ins" can significantly improve the quality of life for AD caregivers. The study, Resources for Enhancing Alzheimer's Caregiver Health II (REACH II), was funded by NIA and NIH's National Institute of Nursing Research and is the first randomized, controlled trial to look at the effectiveness of an AD caregiver support intervention for ethnically diverse populations. Follow-up studies are needed to examine how the intervention might be used through existing community networks of health and aging services.

## Outreach to the Public

Since its inception, NIA has provided the public and health professionals with information about Alzheimer's disease and age-related cognitive change. Twenty-one years ago, Congress established NIA's Alzheimer's Disease Education and Referral (ADEAR) Center to "compile, archive, and disseminate information concerning research, demonstration, evaluation, and training programs and projects concerning AD and related dementias." Today, that mission is being accomplished through a wide variety of materials, resources, and activities for the general public, health professionals, and people with Alzheimer's disease and their families.

ADEAR's programs are active and comprehensive. For example, the number of print materials distributed went from about 377,000 in 2005 to more than 645,000 in 2006. As more and more Americans turn to the Internet for health information, the Center has experienced a striking increase in the number of web visits, up from 1.9 million in 2005 to 2.9 million in 2006. Further, the NIA and ADEAR Center staff, based in Silver Spring, Maryland, proactively invite the public to use its resources. In 2006, the ADEAR Center distributed 43 e-mail alerts to various subscriber lists, letting subscribers know about research news, new publications, and other updates.

The effectiveness in developing information products and strategies is based in part on the NIA's collaborations with agencies, academic institutions, and other organizations. The success of new easy-to-read publications involved collaboration between the ADEAR Center and the NIA's network of Alzheimer's Disease Centers. A new project aims to respond to a lack of materials for the newly emerging audience of people with early-stage AD and their families. In

this effort, ADEAR is working with the Northwestern University School of Medicine's Alzheimer's Research Center to produce a publication *What Happens Next: A Booklet About Being Diagnosed with AD and Related Disorders*. The booklet is actually written by early-stage patients to provide those newly diagnosed with resources and with comfort and support from others who have walked the same path.

## Conclusion

It is difficult to predict the pace of science or to know with certainty what the future will bring. However, the progress we have already made will help us speed the pace of discovery, unravel the mysteries of AD's pathology, and develop safe, effective preventions and treatments, to the benefit of older people and their families.

Thank you for giving me this opportunity to share with you our progress on Alzheimer's disease. I would be happy to answer any questions you may have.